Mechanism and therapeutic prospects of adipose tissue B lymphocytes in obesity and obesity-associated metabolic diseases (Review)

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Abstract. Obesity has become a global epidemic and a notable trigger for numerous chronic diseases, including insulin resistance, type II diabetes, cardiovascular disease, non-alcoholic fatty liver disease and cancer, which is characterized by chronic low-grade inflammation in the adipose tissue. Traditionally, adipose tissue macrophages were considered the central drivers of obesity-associated inflammation; however, studies have revealed that B cells play a notable role in adipose tissue inflammation and metabolic homeostasis. The present review systematically elaborates on the distribution and functions of B cells within adipose tissue, with a focus on the dynamic changes in B cell subsets during the progression of obesity, the mechanisms in promoting metabolic diseases, and the potential applications and challenges of targeting B cells for the treatment of obesity-related metabolic disorders, in order to provide new insights into the mechanistic understanding and therapy of obesity and its associated metabolic diseases.

Contents

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1. Introduction

With rapid economic development and lifestyle changes, obesity has become a notable global public health problem. Since 1990, the prevalence of adult obesity has doubled worldwide, whereas adolescent obesity has tripled (1). According to the latest data released by the World Health Organization in 2022, >1 billion individuals worldwide are affected by obesity, of whom ~65% are adults, 34% are adolescents and <1% are children. This alarming prevalence markedly increases the risk of developing insulin resistance (IR), type II diabetes mellitus (T2DM), cardiovascular disease, non-alcoholic fatty liver disease and various types of cancer, including gastric, esophageal, liver, pancreatic, bladder and breast cancer (1-3). Obesity is more than a simple imbalance between energy intake and expenditure; rather, it arises from complex interactions among genetic, immune and metabolic factors. Elucidating the molecular mechanisms underlying the onset and progression of obesity is therefore of notable importance for both prevention and therapeutic intervention.

Adipose tissue is not merely an energy storage depot but also an active endocrine and immune organ. In addition to adipocytes, it harbors a variety of immune cells, including macrophages, T lymphocytes, B lymphocytes and dendritic cells (4-7). Under conditions of obesity, anti-inflammatory resident immune cells decline, whereas pro-inflammatory immune cells accumulate and become activated, leading to chronic low-grade inflammation in adipose tissue, a key step in the development of obesity-related metabolic disorders. Thus, the immune cell network within the adipose tissue plays a marked role in maintaining tissue homeostasis and metabolic function (8,9). Over the years, the role of B cells in obesity and its associated metabolic complications has attracted increasing attention. B lymphocytes regulate the

adipose tissue immune microenvironment through multiple mechanisms, including interactions with T cells and macrophages, secretion of antibodies such as IgM and IgG, and production of cytokines, including IL-10, TNF-α and IL-6, thereby shaping local inflammatory responses and metabolic homeostasis (10-12). During obesity, B cells in adipose tissue undergo numerical expansion and aberrant activation, thereby exacerbating tissue inflammation and IR. Understanding the heterogeneity, functional diversity and regulatory mechanisms of adipose tissue B cells is essential for unraveling the pathogenesis of obesity and related metabolic diseases. The present review aimed to comprehensively summarize the roles of B-cell subsets in adipose tissue inflammation and metabolic dysregulation during obesity, highlight the underlying mechanisms and discuss the therapeutic potential of targeting B cells in obesity-associated metabolic disorders.

2. Overview of B cells

B-cell subsets and their characteristics. B cells originate from hematopoietic stem cells in the bone marrow and undergo a series of differentiation and maturation processes before participating in immune responses through the secretion of cytokines and antibodies. As a fundamental component of the immune system, they play a notable role in maintaining immune homeostasis and defending against pathogens (13). B cells can be broadly categorized into two major subsets, B-1 and B-2 cells, based on their developmental origins, phenotypic characteristics and functional properties. B-1 cells originate predominantly from fetal liver precursors and represent one of the earliest identified B-cell subsets. They are mainly localized in the pleural and peritoneal cavities, with a smaller proportion residing in the spleen and adipose tissue. In contrast, B-2 cells are primarily derived from adult bone marrow hematopoietic stem cells and are widely distributed in secondary lymphoid organs, including the spleen and lymph nodes. According to CD5 expression, B-1 cells can be further subdivided into $CD5^+$ B-1a and $CD5^-$ B-1b cells. Functionally, B-1a cells rapidly produce natural IgM antibodies with broad reactivity against self and microbial antigens, thereby contributing to early immune defense and immune homeostasis, whereas B-1b cells mainly mediate T cell-independent adaptive immune responses and generate long-lasting protective immunity. In contrast, B-2 cells primarily participate in T cell-dependent immune responses, undergo affinity maturation and class-switch recombination, and predominantly produce high-affinity IgG antibodies, thus playing a central role in adaptive humoral immunity. Although natural antibodies secreted by B-1 cells exhibit relatively low affinity, their polyreactivity and functional diversity enable rapid recognition of a wide spectrum of antigens, making them essential components of the early innate immune system (14).

B-2 cells, also referred to as conventional B cells, progress through stages including pro-B and immature B cells before migrating to the spleen and lymph nodes. There, they further differentiate into follicular B cells (FOB) and marginal zone B cells (MZB) (11). B-2 cells exhibit notable antigen specificity and participate in T cell-dependent humoral immune responses. MZB, located within the splenic marginal sinus, serve as a first line of defense against blood-borne pathogens. FOB, upon antigen stimulation and activation by T follicular helper (TFH) cells, initiate germinal center responses and ultimately differentiate into memory B cells or plasma cells, thereby mediating long-lasting immune protection. In addition, B-2 cells can modulate adaptive immunity through the production of cytokines such as IFN-γ, IL-4 and TNF-α (15). In a healthy immune system, B-1 and B-2 cells reciprocally regulate each other through cytokine signaling and intercellular interactions, thereby maintaining immune homeostasis (16).

Over the years, regulatory B cells (Bregs), a subset of B cells with immunosuppressive functions, have attracted considerable attention. Bregs can arise from various B-cell subsets, including immature B cells, MZB, transitional 2-marginal zone precursor B cells, B-1b cells and plasmablast-like B cells (17-19). Bregs maintain immune tolerance and mitigate inflammation and metabolic dysregulation by secreting immunosuppressive cytokines, including IL-10, IL-35 and transforming growth factor-β (TGF-β). These cytokines regulate T helper 1/2 (Th1/Th2) differentiation, suppress the activity of antigen-presenting cells (APCs) and promote the proliferation of regulatory T cells (Tregs) (20,21).

Distribution of B-cell subsets in adipose tissue under homeostasis. In healthy white adipose tissue of both mice and humans, B-1 cells constitute the predominant B-cell population and play a notable role in maintaining immune homeostasis within adipose tissue. However, precise quantitative data regarding the ratio of B-1 to B-2 cells remain limited, largely due to technical challenges in accurately identifying and distinguishing tissue-resident B-cell subsets. B-1a cells produce natural IgM antibodies and anti-inflammatory cytokines, such as IL-10, which recognize and clear apoptotic cells, oxidized lipids and other self-antigens within adipose tissue, thereby mitigating local inflammatory responses (9,12,22,23). Although B-1b cells secrete lower amounts of IgM, they can alleviate metabolic dysregulation in adipose tissue by suppressing the pro-inflammatory responses of M1 macrophages (24,25). In adipose tissue under homeostatic conditions, conventional follicular B-2 cells are relatively sparse; however, certain B-2 cell subsets with functional similarities to B-1 cells contribute to the maintenance of adipose tissue homeostasis through the production of natural IgM (26). Similar to FOB, MZB are also present at low frequencies in adipose tissue, but their innate capacity for rapid responses to blood-borne antigens enables them to participate in local immune surveillance. In addition, a small population of Bregs with immunosuppressive functions may exist within homeostatic adipose tissue. By producing anti-inflammatory factors such as IL-10 and cooperating with Tregs, these Bregs help suppress local inflammatory responses and maintain immune equilibrium, thereby playing a notable role in preserving white adipose tissue homeostasis (27). However, their precise proportion and phenotypic characteristics within homeostatic adipose tissue remain to be elucidated (Fig. 1).

In adipose tissue, B cells are not randomly dispersed but instead form loose aggregates through interactions with macrophages, T cells and innate lymphoid cells (ILCs). These structures are referred to as fat-associated lymphoid clusters (FALCs). FALCs represent a form of tertiary lymphoid structure that was initially identified in the mesenteric adipose

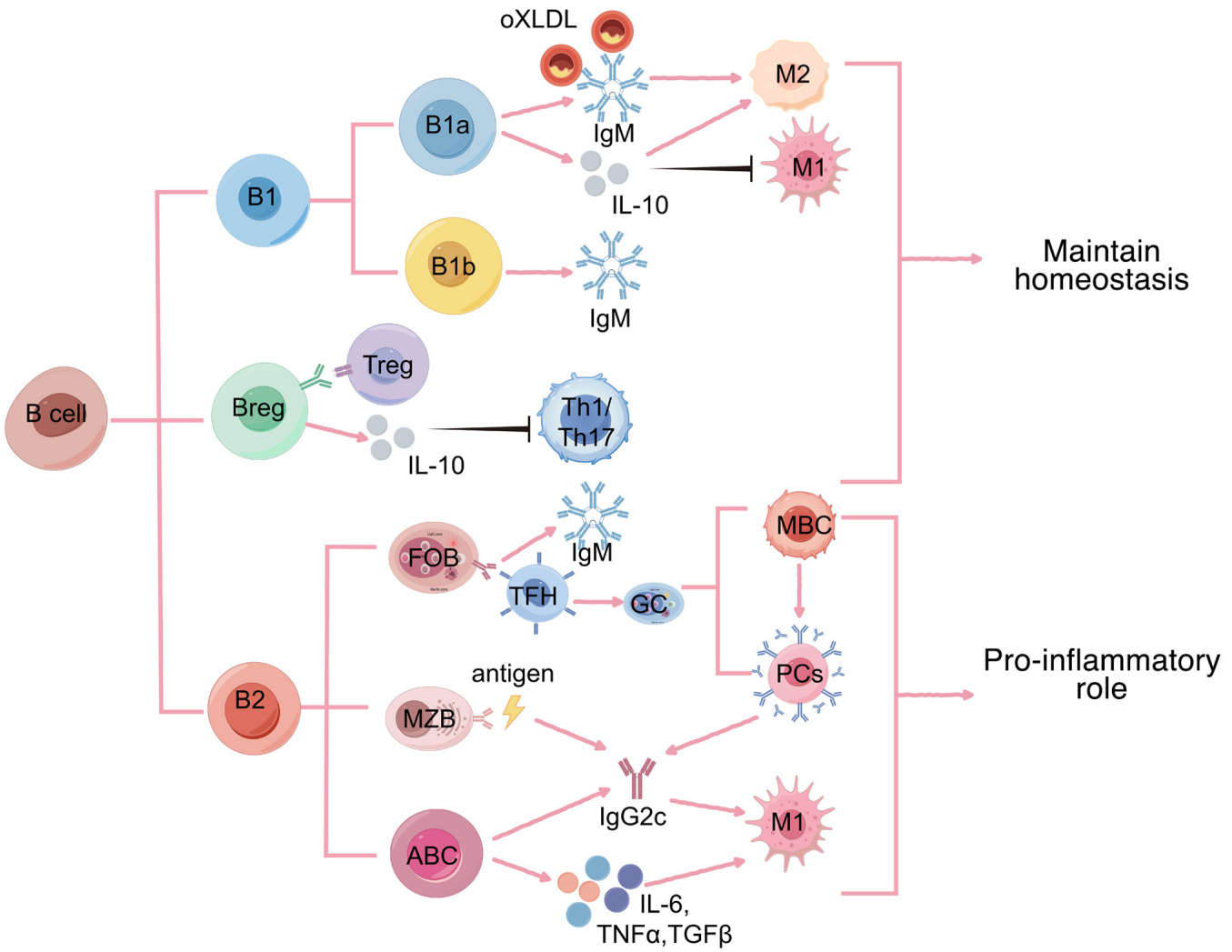

Figure 1. Functions of B-cell subsets in adipose tissue. Under physiological conditions, B-1 cells constitute a major population of B cells in adipose tissue and can be further subdivided into B-1a and B-1b subsets. B-1a cells predominantly secrete natural IgM, which recognizes and clears oxidized low-density lipoprotein and produce the anti-inflammatory cytokine IL-10, promoting macrophage polarization toward the M2 phenotype while suppressing M1 activation, thereby exerting anti-inflammatory effects. B-1b cells also mainly secrete IgM, contributing to innate immune defense and the maintenance of tissue homeostasis. Bregs, through IL-10 secretion and cooperation with Tregs, suppress the proportion and effector functions of Th1/Th17 cells, thereby inhibiting inflammatory responses. Under obese conditions, B-2 cells become the predominant B-cell population in adipose tissue and can further differentiate into FOB, MZB and ABCs. Upon antigen stimulation and with the help of Tfh cells, FOB cells enter germinal centers and differentiate into MBCs and PCs, producing IgM or undergoing class-switch recombination. MZB cells rapidly respond to antigenic stimulation and contribute to the production of pro-inflammatory antibodies, such as IgG2c. ABCs, characterized by senescence-associated phenotypes and strong pro-inflammatory features, preferentially produce autoreactive antibodies (such as IgG2c) and secrete pro-inflammatory cytokines, including IL-6, TNF-α and TGF-β, thereby promoting M1 macrophage activation and amplifying adipose tissue inflammation. Collectively, these pro-inflammatory B-cell responses drive the development of chronic inflammation. Pink arrows indicate stimulation or activation; black arrows indicate inhibition or downregulation. B reg, B regulatory cell; Treg, T regulatory cell; Th, T helper cell; FOB, follicular B cells; ABCs, age-associated B cells; MZB, marginal zone B cells; tfh, T follicular helper; MBCs, memory B cells; PCs, plasma cells.

tissue of both mice and humans (28), and B cells constitute one of the central cellular components of FALCs (29).

3. Alterations and mechanisms of B-cell subsets in obesity

Under metabolic perturbations such as obesity, the adipose tissue microenvironment undergoes notable remodeling, leading to the disruption of immune homeostasis. In this context, marked alterations are observed in B-cell abundance, spatial organization and functional phenotypes. Although accumulating evidence suggests that obesity-associated B-cell changes are generally characterized by enhanced pro-inflammatory activity accompanied by impaired immunoregulatory capacity, these findings are not entirely consistent across different experimental models, species or adipose depots, highlighting a pronounced context-dependent regulation. In high-fat diet (HFD)-induced obese C57BL/6J mice, both the number and size of FALCs are markedly increased within visceral adipose tissue (VAT) (29,30). Concomitant with the expansion of FALCs, a substantial number of B cells are recruited from the circulation and bone marrow into adipose tissue, resulting in an increase in the proportion of B cells within the stromal vascular fraction from ~10% in lean conditions to ~20% in obesity. These recruited cells predominantly exhibit a conventional B-2 cell phenotype (31). In addition to white adipose tissue, an increased proportion of B cells has also been observed in murine brown adipose tissue (BAT) under HFD conditions; however, the precise functional roles of

B cells in BAT remain largely undefined (32). To date, studies addressing B-cell function within BAT are notably limited, and it remains unclear whether these cells actively participate in metabolic regulation or merely reflect the spillover of systemic inflammation. Consequently, this area represents a substantial gap in current knowledge. Of note, in human adipose tissue, systematic quantitative analyses of B-cell abundance and spatial distribution are still lacking, which substantially constrains the direct extrapolation of findings derived from animal models.

In VAT, B-cell accumulation occurs at an early stage of obesity. As early as 4 weeks of HFD feeding, both B-1 and B-2 cell numbers are markedly increased in murine epididymal adipose tissue (33). However, despite the numerical expansion of B-1 cells, their functional protective properties, such as the production of natural IgM, are often attenuated in obesity settings, suggesting that the obesogenic microenvironment may drive a state of functional exhaustion in B-1 cells. In parallel, pro-inflammatory B-2 cells and T-bet$^+$CD21$^-$CD23$^-$ age-associated B cells (ABCs) progressively accumulate during weight gain in mice and with increasing body mass index (BMI) in humans (14,34,35). Concomitantly, B cell-derived antibody profiles shift from predominantly protective IgM toward pathogenic IgG isotypes. These ABCs are hypothesized to exacerbate chronic inflammation and IR by promoting IgG antibody production and pro-inflammatory cytokine secretion. Nevertheless, in human studies, the definition of ABCs remains heterogeneous, and direct evidence for their presence and functional relevance within adipose tissue is still limited (36).

In human studies, data regarding Breg subsets remain relatively limited. Available evidence indicates that patients with T2DM exhibit reduced Breg frequencies and IL-10 production in the peripheral blood and certain tissues (37-40), suggesting a compromised immunosuppressive capacity. However, most of these studies are cross-sectional in nature, and can therefore not establish whether alterations in Bregs are a cause or a consequence of metabolic dysregulation. Furthermore, findings derived from peripheral blood may not fully reflect the local immune landscape within adipose tissue.

By contrast, murine studies have provided stronger causal support for the protective role of Bregs, as the adoptive transfer of Bregs has been shown to ameliorate adipose tissue inflammation and IR in diet-induced obesity (DIO) models. Mechanistically, obesity-associated chronic inflammation and the senescence-associated secretory phenotype have been implicated in driving B-cell polarization toward pro-inflammatory phenotypes while suppressing Breg function through sustained activation of the NF-κB and Janus kinase-signal transducer and activator of transcription (JAK/STAT) signaling pathways (10,41,42). In addition, the persistent activation of the p38 mitogen-activated protein kinase (p38/MAPK) and protein phosphatase 2A signaling pathways disrupts the balance between B-cell proliferation and differentiation, thereby impairing the maintenance of Breg function (43).

FALCs are considered notable microenvironmental niches that support aberrant B-cell expansion and activation in obesity. Under homeostatic conditions, M2-polarized macrophages promote the recruitment of B-1 cells into adipose tissue through the secretion of C-X-C motif chemokine ligand 13 (CXCL13) (44,45). In the obese state, group 2 ILCs within mesenteric adipose tissue-associated FALCs secrete IL-5, thereby enhancing natural IgM production by B-1 cells and potentially exerting metabolically protective effects. However, with the progression of obesity, sustained increases in CXCL13, IL-7 and other stromal-derived factors from adipocyte progenitors and fibroblasts drive excessive B-cell recruitment and activation. Activated B cells, in turn, reinforce chemokine production by stromal cells, establishing a positive feedback loop between B cells and the stromal compartment that promotes pathological FALC expansion and the maintenance of chronic inflammation (46). In aged mice, the reduced mRNA stability of E47 (TCF3) in visceral adipose tissue impairs activation-induced cytidine deaminase-mediated somatic hypermutation and class-switch recombination, leading to defective germinal center responses and limited antibody affinity maturation. These alterations collectively contribute to obesity-associated inflammation and immune dysregulation (47). Nevertheless, most of the available evidence is derived from global knockout or pharmacological intervention models, making it difficult to disentangle B-cell-intrinsic effects from systemic inflammatory changes.

Inflammatory cytokines exert a 'double-edged sword' effect on B-cell chemotaxis and functional remodeling. In obese mice, adipocytes within VAT secrete a range of chemokines, including CXCL10, C-C motif chemokine ligand 2 (CCL2) and CCL5, which preferentially recruit B-2 cells through their corresponding receptors, such as C-C motif chemokine receptor 2 (CCR2) and CCR3 (11,48). In HFD mice, the lipid-derived inflammatory mediator leukotriene B4 promotes the recruitment of B-2 cells into adipose tissue via leukotriene B4 receptor 1 and directly induces a pro-inflammatory B-cell phenotype. This, in turn, exacerbates IR through the activation of CD4$^+$ and CD8$^+$ T cells as well as M1-polarized macrophages (31). IL-6 and TNF-α, produced by both adipocytes and B cells, are widely recognized as key drivers of pro-inflammatory B-cell polarization (15,49). Of note, IL-6 exhibits context-dependent effects, as it has also been shown to improve lipid metabolism and insulin sensitivity in murine models (50,51). In addition, the IL-6 family member cardiotrophin-like cytokine factor 1 is upregulated in the BAT of obese mice and suppresses mitochondrial biogenesis and thermogenic capacity by activating STAT3 and inhibiting PGC-1α/β transcription, thereby promoting BAT 'whitening', as indicated by adipocyte hypertrophy, lipid droplet accumulation, uncoupling protein 1 (UCP-1) suppression, and mitochondrial dysfunction, initiates and accelerates obesity progression (52). In patients with T2DM, TNF-α acts as a major driver of adipose tissue inflammation by inducing immune cell polarization and suppressing regulatory immune functions. Furthermore, TNF-α enhances lipolysis and increases free fatty acid release, further aggravating IR (53).

Adipocytes not only serve as energy storage units, but also function as endocrine cells, secreting a variety of adipokines that play notable regulatory roles in B-cell biology. In obese individuals, leptin, a key adipocyte-derived hormone, is positively associated with BMI. B cells express leptin receptor (LEPR/Ob-Rb) on their surface, and leptin binding activates B cells from both young and elderly peripheral blood, inducing the

secretion of pro-inflammatory cytokines, including IL-6 and TNF-α, primarily through the activation of the JAK2/STAT3 and p38 MAPK/ERK1/2 signaling pathways (54,55). In addition, in obese individuals, leptin secreted by adipose tissue mediates the metabolic reprogramming of B cells through the activation of the mechanistic target of rapamycin complex 1 pathway, enhancing glycolytic and biosynthetic activity and driving differentiation toward a pro-inflammatory phenotype. This is characterized by the upregulation of CD25 and human leukocyte antigen DR expression and increased secretion of IL-6 and TNF-α (56). Clinical studies have indicated that adiponectin levels are reduced in obese individuals, and that exerts anti-inflammatory effects by inhibiting AMP-activated protein kinase signaling, thereby enhancing signal transduction and STAT3 activity to promote IL-10 transcription (57-59). Furthermore, adiponectin can induce B1 cells to secrete the peptide inhibitor of transendothelial migration, derived from the 14-3-3ζδ protein, which modulates endothelial adhesion molecules and sphingosine-1-phosphate signaling, thereby limiting T-cell trafficking and inflammatory responses (60,61). In HFD-fed mice, adiponectin indirectly suppresses the pro-inflammatory phenotype of B cells through multilayered immunoregulatory mechanisms. On one hand, adiponectin upregulates Sirtuin 1 and peroxisome proliferator-activated receptor γ whereas inhibiting the Th17 lineage-specifying transcription factor retinoic acid-related orphan receptor γt markedly suppressing Th1 and Th17 differentiation and pro-inflammatory cytokine production, and concurrently promoting FoxP3 expression; this leads to an expansion of the number and function of Tregs, which shifts immune responses toward tolerance. On the other hand, adiponectin remodels dendritic cell phenotypes by downregulating major histocompatibility complex (MHC) class II and costimulatory molecules CD80/CD86, suppressing the secretion of pro-inflammatory cytokines such as IL-12, and upregulating inhibitory molecules such as programmed cell death ligand 1 (PD-L1). This attenuates the dendritic cell-mediated activation of effector T cells while promoting Treg induction. Within this immunoregulatory environment, Treg-mediated suppression and reduced pro-inflammatory T-cell responses collectively constrain aberrant B-cell activation and pro-inflammatory function, thereby indirectly limiting B-cell inflammatory phenotypes (62-64). Furthermore, obesity-associated hyperglycemia, cell death and lipid spillover can activate antigen-specific B cells, leading to their expansion and pathogenic antibody production. In db/db mice, elevated glucose concentrations inhibit IgM secretion by B-1 cells and promote apoptosis (65). Free fatty acids, such as palmitate, enhance B-cell IL-10 secretion and survival in adipose tissue via Toll-like receptor 4 (TLR4) signaling, indicating that tissue-derived metabolic cues regulate the fate of B-cell (21,38).

The 'gut-adipose axis' also plays a notable role in B-cell immunoregulation (66). High-fat diets alter the gut microbiota in humans and mice, compromise intestinal barrier integrity and lead to endotoxemia, which activates adipose tissue B cells and induces the expansion of IL-10$^+$ Breg cells (57,67). In DIO mice, gut-derived lipopolysaccharide (LPS) activates the TLR4-myeloid differentiation primary response 88-NF-κB signaling pathway, inducing the high expression of pro-inflammatory cytokines such as TNF-α and IL-6, thereby amplifying B-cell–mediated inflammatory responses. Although fatty acids themselves are not direct TLR4 ligands, they can indirectly activate this pathway by promoting LPS translocation or altering cellular metabolism, exacerbating B-cell inflammatory activation (68-70). Peritoneal B-1a cells aberrantly activated by commensal bacteria promote insulin resistance (IR) by enhancing systemic and adipose tissue inflammation, facilitating macrophage polarization toward the pro-inflammatory M1 phenotype, and impairing insulin signaling through sustained activation of inflammatory pathways, including NF-κB, JNK and p38 MAPK; following bariatric surgery, the gut microbiota shifts toward a lean phenotype, characterized by reduced adiposity, improved insulin sensitivity, normalized glucose metabolism, and attenuated inflammatory responses, thereby restoring adipose tissue B-cell function (58,71). Obesity also reduces the number of intestinal IgA$^+$ B cells and decreases secretory IgA levels (66), IgA deficiency accelerates B-cell senescence, leading to impaired B-cell function and increased autoantibody production, further aggravating glucose intolerance and reducing insulin sensitivity. In addition, in obesity settings, elevated 25-hydroxycholesterol levels in Peyer's patches inhibit antigen-specific IgA$^+$ B-cell differentiation, whereas cholesterol-25-hydroxylase deficiency alleviates this effect (72) (Fig. 2).

Collectively, current evidence supports that obesity drives B-cell dysfunction through the synergistic actions of inflammatory cytokines, adipokines, metabolic products and gut microbiota, thereby promoting chronic adipose tissue inflammation and metabolic dysregulation. However, most mechanistic conclusions are primarily based on murine models, and the temporal relationships, causality and tissue specificity in humans remain incompletely elucidated. Further integrative multi-omics and functional validation studies are warranted to address these knowledge gaps.

4. Roles and mechanisms of B cells in obesity-related metabolic diseases

In obesity-related metabolic diseases, adipose tissue B cells are increasingly recognized as a notable regulatory node linking immune inflammation and metabolic dysregulation. Accumulating evidence indicates that, under obese conditions, aberrantly activated B cells engage in complex interactions with adipocytes, T cells and macrophages through antigen presentation, cytokine secretion and antibody production, thereby exacerbating adipose tissue inflammation and promoting IR (10). Clinical studies have shown that patients with T2DM exhibit increased B-cell activation in peripheral blood, accompanied by elevated secretion of inflammatory mediators such as IL-8, which is closely associated with chronic inflammatory responses (39,73). In aged mice, the local depletion of VAT-resident B cells markedly improves insulin sensitivity (5). Under HFD conditions, the deletion of the B cell-specific Oct co-activator from B cells, a key regulator of B-cell development, notably ameliorates adipose tissue inflammation and IR in mice (74,75). Similarly, the deletion of the inhibitor of DNA binding 3 gene increases B-1 cell abundance in white adipose tissue, leading to reduced adipose inflammation and improved glucose tolerance (24). Adoptive transfer of B-1 cells into HFD-fed B cell-deficient

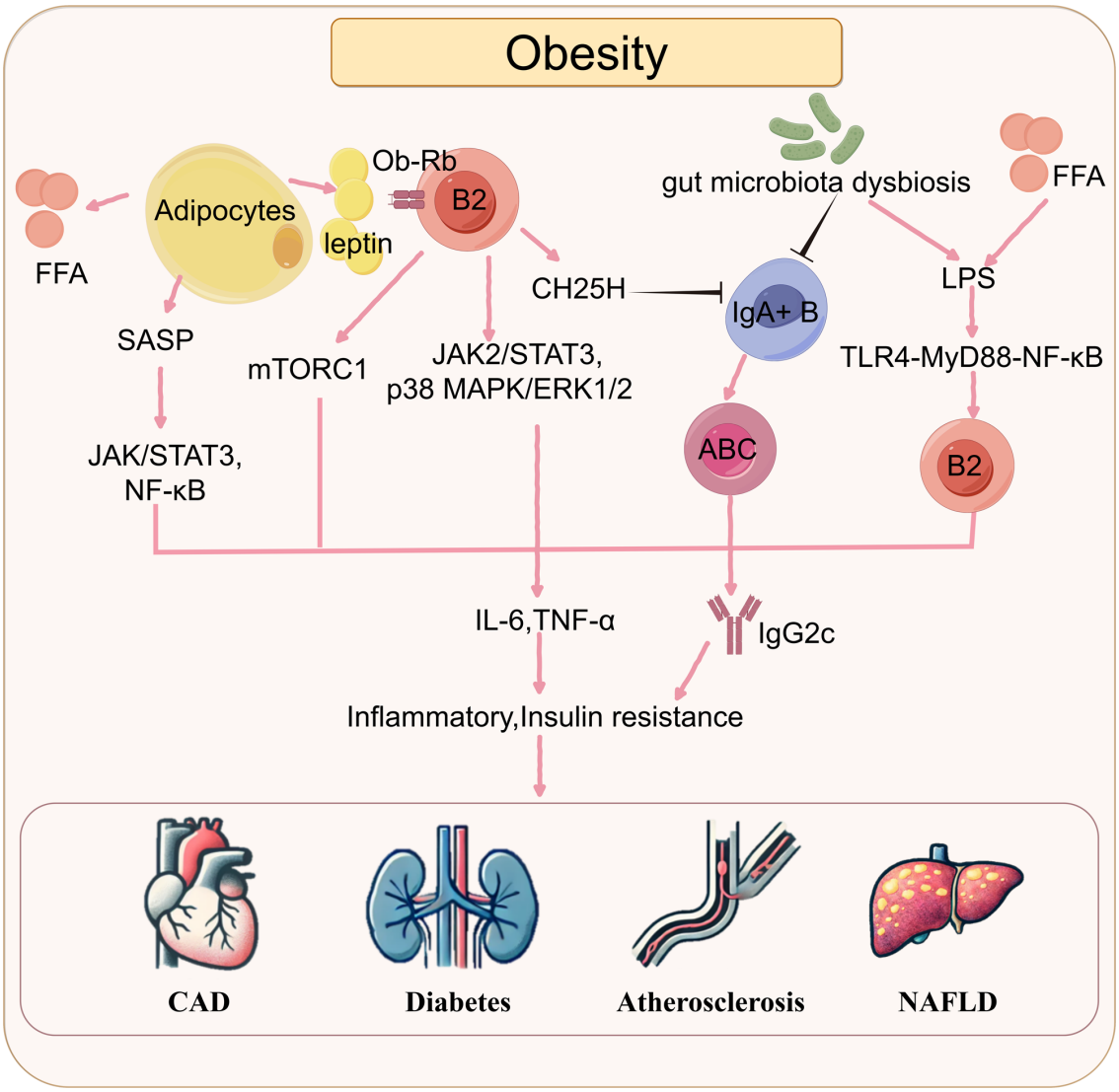

Figure 2. Adipose tissue microenvironment promotes B-cell functional reprogramming and regulates metabolic inflammation. Under obese conditions, enhanced lipolysis in adipocytes leads to elevated levels of FFAs, accompanied by increased leptin secretion and the formation of SASP. Leptin acts on B-2 cells via its receptor Ob-Rb, activating mTORC1 as well as the JAK2/STAT3 and p38 MAPK/ERK1/2 signaling pathways, thereby promoting pro-inflammatory activation of B-2 cells. SASP simultaneously activates the JAK/STAT3 and NF-κB pathways, amplifying inflammatory signaling. Moreover, obesity-associated gut dysbiosis and high FFA levels increase LPS levels in adipose tissue. LPS, through the TLR4-MyD88-NF-κB signaling axis, promotes B-2 cell expansion and inflammatory responses. At the same time, B-2 cells increase the synthesis and secretion of CH25H, which inhibits the differentiation and maintenance of IgA^+ B cells, further impairing the intestinal IgA barrier. The reduction in IgA^+ B cells also promotes B-cell senescence, increasing the proportion of ABCs and the secretion of IgG2c antibodies, thereby exacerbating inflammation. These converging signaling pathways collectively elevate levels of pro-inflammatory cytokines such as IL-6 and TNF-α, inducing chronic adipose tissue inflammation and aggravating insulin resistance, ultimately contributing to the development of CAD, diabetes, atherosclerosis and NAFLD. Pink arrows indicate stimulation or activation; black arrows indicate inhibition or downregulation. FFA, free fatty acid; LPS, lipopolysaccharide; ABCs, associated B cells; NAFLD, non-alcoholic fatty liver disease; CAD, coronary artery disease; SASP, senescence-associated secretory phenotype.

obese mice also alleviates VAT inflammation and improves IR (12). Collectively, these findings provide direct evidence of the pathogenic role of adipose tissue B cells in metabolic homeostasis disruption; however, the applicability of these strategies in humans remains to be determined.

Studies have further demonstrated that distinct B-cell subsets exert divergent effects on adipose tissue and cardiovascular homeostasis. In HFD-fed apolipoprotein E $(Apoe)^{-/-}$ mice, B-1a and B-1b cells secrete natural IgM antibodies in the spleen and adipose tissue to neutralize oxidized low-density lipoprotein (oxLDL) and promote macrophage polarization toward an anti-inflammatory phenotype, thereby suppressing myocardial inflammation and atherosclerosis. By contrast, B-2 cells secrete TNF-α, IL-6 and TGF-β, activate cardiac fibroblasts and promote collagen deposition and ventricular remodeling (11,76). In addition, B cells can modulate T-cell responses by promoting pro-atherogenic Th1 immunity while suppressing anti-atherogenic interleukin-17 production, thereby accelerating atherosclerosis progression (77). Clinical and experimental studies have also revealed the presence of large B-cell clusters in epicardial adipose tissue of patients with coronary artery disease (78). Of note, as early as 3 days after myocardial infarction, B-cell numbers are markedly increased in murine pericardial adipose tissue, with no notable

changes observed in the myocardium itself, suggesting that local B-cell proliferation is the predominant source. These B cells secrete granulocyte-macrophage colony-stimulating factor (GM-CSF), which promotes the recruitment and maintenance of dendritic cells in pericardial adipose tissue and accelerates post-infarction fibrosis (79).

Adipose tissue B cells further contribute to metabolic dysfunction by releasing pathogenic IgG antibodies and inflammatory mediators, thereby promoting monocyte infiltration into FALCs and sustaining the release of pro-inflammatory factors, ultimately leading to adipose tissue dysfunction and metabolic imbalance (11,80). In obese mice, B-2 cell infiltration into mesenteric adipose tissue precedes that of T cells and macrophages (81). In HFD-induced obese mice, activated B cells produce large amounts of pro-inflammatory cytokines, including TNF-α and GM-CSF, which recruit macrophages and promote their differentiation toward an inflammatory phenotype, thereby inducing IR (33,82). During obesity, B cells within FALCs become activated and function as APCs, presenting internalized lipids or other antigens to TFH cells. TFH cells subsequently provide key costimulatory signals, such as CD40L and IL-21, thereby promoting B-cell differentiation into plasma cells and driving the production of pro-inflammatory Immunoglobulin G2c (IgG2c) antibodies. These IgG2c antibodies accumulate within adipocyte crown-like structures, where they form immune complexes with oxidatively modified lipoproteins (such as oxLDL) or adipose tissue-derived self-antigens. The resulting immune complexes activate macrophages through Fc γ receptor receptors, thereby amplifying adipose tissue inflammation. Of note, the adoptive transfer of IgG isolated from DIO mice into B cell-deficient mice is sufficient to induce macrophage polarization toward the M1 phenotype, leading to the increased production of pro-inflammatory mediators (33,39,83). Furthermore, B cell-derived IgG can drive Th1/Th2 polarization through MHC-dependent mechanisms, leading to the secretion of TNF-α and IFN-γ, which further stimulate B cells and establish a positive feedback loop that exacerbates IR and adipose tissue inflammation (84).

In metabolic diseases such as obesity and diabetes, both the number and function of Bregs are markedly reduced, resulting in decreased IL-10 production, impaired anti-inflammatory capacity, increased release of pro-inflammatory factors and exacerbation of adipose tissue inflammation and IR (85). By contrast, in autoimmune diseases and cancer, B-1 and Breg cells can exert anti-inflammatory effects by expressing immune checkpoint molecules, such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and CD39/CD73, and by secreting IgM antibodies and IL-10 (86). Of note, infection with *Schistosoma japonicum* induces a marked upregulation of IL-10 production in $CD19^+CD9^+$ B cells, promoting the expansion of Tregs and Th2 cells, while reducing Th1 and Th17 responses. This immune shift alleviates inflammation and improves insulin sensitivity in HFD-fed mice, suggesting that enhancing $CD9^+$ B cells or IL-10-producing Breg function may represent a novel strategy for modulating obesity-associated inflammation and metabolic dysregulation (87,88). Consistently, studies have demonstrated that in HFD-fed mice and patients with T2DM, IL-10 suppresses pro-inflammatory cytokine production through the activation of the STAT3 signaling pathway, promotes Treg differentiation, induces macrophage polarization toward the M2 phenotype, protects adipose tissue from inflammation and counteracts IR (23,89,90).

In summary, B cells exert dual pro- and anti-inflammatory roles in obesity-related metabolic diseases. While pathogenic B-cell responses exacerbate inflammation and metabolic dysfunction, protective B-cell subsets contribute to the maintenance of metabolic homeostasis. These findings provide a theoretical basis for the development of B cell-targeted therapeutic strategies in metabolic diseases (91,92).

5. Targeting B cells as a therapeutic strategy in obesity and obesity-related metabolic diseases

Direct B-cell-depleting therapeutic strategies have been widely applied in the treatment of B-cell non-Hodgkin lymphoma and autoimmune diseases such as rheumatoid arthritis (93). Given the pivotal role of B cells in obesity-associated chronic inflammation and metabolic dysregulation, B-cell-targeted interventions are increasingly recognized as a potential metabolic therapeutic strategy. Although current evidence is largely derived from animal models and studies conducted in other disease contexts, these findings provide an important theoretical foundation for the application of B-cell-targeted therapies in obesity-related metabolic disorders.

CD20-mediated B-cell depletion. Rituximab is the first clinically approved anti-CD20 monoclonal antibody and selectively depletes mature B cells while sparing plasma cells and B-cell precursors (94). In murine models of obesity, CD20-mediated B-cell depletion predominantly affects pro-inflammatory B-2 cells, whereas B-1 cells are relatively preserved. This intervention also reduces C-C motif chemokine ligand 7-mediated monocyte recruitment, thereby attenuating tissue inflammation, highlighting its potential therapeutic value in obesity-associated metabolic dysfunction (77,95). In human studies, although CD20-targeted therapies have not been directly applied to obesity or metabolic diseases, multiple preclinical investigations have demonstrated that this strategy markedly reduces B-2 cell numbers and delays the progression of atherosclerosis. The underlying mechanisms may involve the suppression of B-cell-dependent monocyte recruitment to the vasculature or enhancement of immunosuppressive dendritic cell populations and Tregs (96,97). These findings suggested that selectively depleting pro-inflammatory B-2 cells while preserving B-cell subsets with immunoregulatory functions may represent a key advantage of B-cell-targeted therapies. However, systemic B-cell depletion is known to be associated with adverse effects, including increased infection risk and hypogammaglobulinemia, in the treatment of autoimmune diseases and lymphomas (98,99). When considered for chronic metabolic diseases, long-term safety profiles constitute a primary concern. Furthermore, non-selective depletion of most B-2 cells may also compromise beneficial Breg populations, potentially leading to immune homeostasis imbalance (100,101).

Targeting the B-cell activating factor (BAFF)/a proliferation-inducing ligand (APRIL) system. BAFF, a member of

the TNF ligand family, is a notable cytokine required for B-cell survival and maturation. Under metabolic dysregulation conditions such as obesity and IR, BAFF can be secreted by multiple immune cell types (102). Among BAFF-related pathways, the BAFF/APRIL system plays a central role in the survival and proliferation of B-2 cells. Kim *et al* (103) and Sanchez *et al* (104) demonstrated that circulating BAFF levels are positively associated with IR and endothelial dysfunction in obese individuals, providing clinical evidence for its pathogenic role in metabolic diseases. In systemic lupus erythematosus (SLE) mouse models, excessive BAFF drives the expansion of inflammatory B-2 cells and synergizes with B-cell receptor and TLR signaling pathways to amplify B-cell responses, thereby promoting the production of pathogenic antibodies and pro-inflammatory cytokines such as IL-6 and TNF-α (102,105). Furthermore, the primary BAFF-shedding enzyme A disintegrin and metalloproteinase 17 is markedly activated in $Apoe^{-/-}$ mice fed an atherogenic diet, further enhancing BAFF-associated pro-inflammatory signaling (106). Nevertheless, BAFF also exhibits functional duality in metabolic diseases; some studies have shown that in mice fed a HFD for 8 weeks, decreased BAFF levels are accompanied by increased adipose tissue inflammation, suggesting that BAFF may exert protective effects during early disease stages by maintaining Breg survival and immune tolerance (38,102,105). Therefore, the role of BAFF appears to be both stage- and dose-dependent.

Based on these mechanisms, treatment with BAFF-neutralizing monoclonal antibodies (such as single-stranded DNA-binding protein 2) and BAFF receptor (BAFFR) has been shown to reduce overall B-cell numbers and selectively deplete B-2 and plasma cells. Belimumab, a monoclonal antibody targeting BAFF, is the first drug approved in nearly 60 years for the treatment of SLE (107). Other agents targeting the BAFF/APRIL system, including the BAFF inhibitor blisibimod, the BAFFR-targeting antibody ianalumab and the fusion protein atacicept, composed of the Ig fragment of transmembrane activator and CAML interactor (TACI) and capable of binding both BAFF and APRIL (108), have not yet entered routine clinical use. Of note, the BAFF/APRIL system is essential for B-cell homeostasis, primarily through its interactions with BAFF-R, TACI and BCMA, which collectively regulate B-cell survival, differentiation and antibody production. BAFF-R signaling is critical for the maintenance of transitional and mature naïve B cells, whereas TACI and BCMA control humoral immune responses, immunoglobulin class-switch recombination and long-lived plasma cell survival. These effects are mainly mediated by activation of the non-canonical NF-κB2 pathway, together with PI3K/Akt and MAPK signaling cascades. Moreover, BAFF availability serves as a key checkpoint during B-cell development and peripheral selection, thereby maintaining immune homeostasis (108,109). BAFF may also exert B-cell-independent anti-inflammatory effects through binding to TACI expressed on myeloid cells, and its long-term inhibition may impair humoral immune defense and increase susceptibility to infections (106). Animal studies have shown that BAFF deficiency can exacerbate atherosclerosis by disrupting TACI signaling in myeloid cells, which activates pro-inflammatory pathways (TLR9-IRF7), increases CXCL10 and IFIT2 expression, and promotes both local plaque inflammation and systemic immune activation, leading to larger, less stable plaques (106). Therefore, the long-term efficacy and safety of targeting the BAFF/APRIL pathway in chronic metabolic diseases must be carefully evaluated. The development of tissue-specific or subset-selective intervention strategies may represent a safer therapeutic direction.

Exploratory strategies targeting costimulatory signals and B-cell functional regulation. The CD40-CD40L pathway represents an notable costimulatory signal required for full B-cell activation. Its blockade suppresses pathological interactions between B cells and T cells, thereby reducing aberrant antibody production and inflammatory amplification loops (110). Under HFD conditions, the genetic deficiency of CD40L attenuates diet-induced obesity, hepatic steatosis and systemic IR in mice (111). In studies on atherosclerosis, preclinical evidence from CD40- or CD40L-deficient models generally supports a pro-atherogenic role of this signaling axis. However, despite the widely accepted view that T-cell-dependent and CD40-dependent B-cell responses promote the progression of atherosclerosis, elevated levels of circulating $CD40^+$ B cells have been associated with a reduced risk for stroke. This seemingly paradoxical observation is thought to be associated with the marked role of CD40 signaling in Breg differentiation (112-114). It should be noted that CD40 signaling plays a central regulatory role in multiple immune functions, and systemic inhibition may compromise host immune defense, weaken vaccine responses and increase susceptibility to infections (111). Consequently, any therapeutic intervention targeting CD40 must be approached with caution.

Aberrant B-cell activation in obesity is also extensively regulated by metabolic and inflammatory microenvironments (10). Studies have shown that the adoptive transfer of $T\text{-}bet^+$ B cells exacerbates metabolic dysfunction in obese mice, whereas the B-cell-specific deletion of T-box transcription Factor 21 reduces serum IgG2c levels, inflammatory cytokine production and inflammatory macrophage accumulation in adipose tissue, thereby alleviating metabolic abnormalities (35). In addition, mice with B-cell-specific Tlr9 deficiency exhibit increased adipose tissue inflammation, weight gain and impaired glucose and insulin tolerance (115). These findings indicated that selectively targeting $T\text{-}bet^+$ B cells or modulating TLR9 signaling pathways may offer therapeutic benefits for improving obesity-associated metabolic homeostasis in animal models.

Overall, multiple B-cell-targeted strategies have demonstrated potential value in ameliorating inflammation and metabolic abnormalities in animal models and related disease contexts. However, with the exception of a limited number of murine studies (33,116), robust clinical evidence supporting the efficacy of B-cell depletion or costimulatory molecule-targeted therapies in obesity-induced type II diabetes and IR is lacking. Future studies using disease models more closely related to human pathology and well-designed prospective clinical trials are required to systematically evaluate long-term efficacy, safety and appropriate patient populations.

5. Summary and perspectives

Adipose tissue B cells have emerged as key drivers of obesity-associated metabolic diseases, shifting from protective regulators under homeostatic conditions to pathogenic 'disruptors' in the obese state. Through both antibody-dependent and antibody-independent mechanisms, B cells promote chronic adipose tissue inflammation and metabolic dysregulation. Targeting B cells, particularly specific pathogenic subsets or functional programs, therefore represents a promising therapeutic avenue for the treatment of obesity and its related complications.

Future studies should prioritize the establishment of comprehensive human adipose tissue B-cell atlases, coupled with an in-depth characterization of the heterogeneity of adipose tissue B-cell subsets. Elucidating the molecular mechanisms through which distinct B-cell populations contribute to obesity-associated metabolic diseases will be essential for the precise targeting of pathogenic B-cell subsets, such as ABCs, while preserving protective populations including B-1 cells and Bregs. In parallel, efforts should be directed toward accelerating the clinical translation of these insights.

In conclusion, as notable regulators within the adipose tissue immune microenvironment, B cells play a central role in shaping obesity-related inflammatory responses. A deeper understanding of their functional diversity not only advances our mechanistic insight into obesity-associated inflammation but also provides an important theoretical foundation and practical guidance for the development of more precise and safer immunometabolic therapeutic strategies.

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Availability of data and materials

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Authors' contributions

HW and HL contributed to the writing of the original draft and manuscript design. XZ participated in the literature search, analysis and manuscript design. LW and ML were responsible for reviewing and editing the manuscript, as well as funding acquisition. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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